PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gilles GUICHARD et al.

Serial No. (unknown)

Filed herewith

NOVEL STABILIZED ACTIVATED DERIVATIVES OF CARBAMIC ACID, THEIR PROCESS OF PREPARATION AND THEIR USE FOR THE PREPARATION OF UREAS

PRELIMINARY AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to the first Official Action and calculation of the filing fee, please amend the above-identified application as follows:

IN THE CLAIMS:

Amend claim 3 as follows:

--3. (amended) Process according to claim 1, in which the structure of the activated derivative of carbamic acid is conferred by the N-hydroxysuccinimide group.

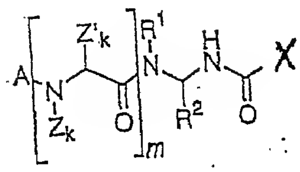
Amend claim 9 as follows:

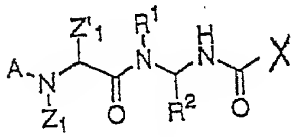
--9. (amended) Compounds according to claim 7, having the formula (I bis)

Amend claim 10 as follows:

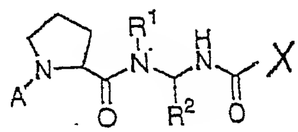
--10. (amended) Compounds according to claim 7, having the following formulas:

n=1

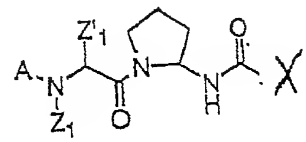




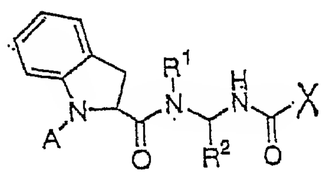
m =1



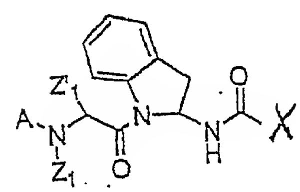
m =1



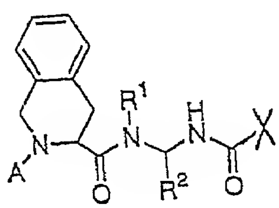
m =1



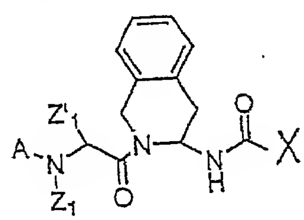
m =1



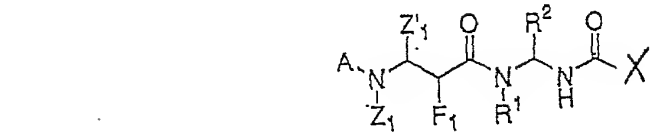
m =1



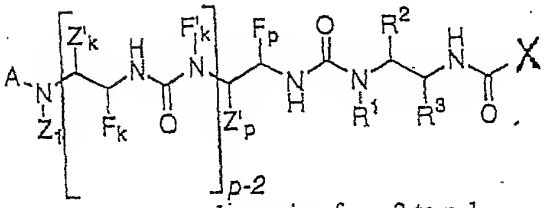
m =1



m =1

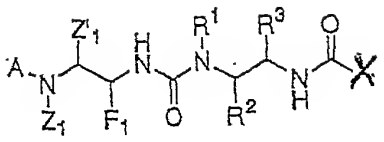


n=2

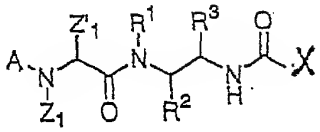


p-2

k varying from 2 to p-1



p=1



in which

- m and p are comprised from 1 to 10,

- A represents either a protective group selected from the following groups: a hydrogen atom, an oxycarbonyl (ROCO) group, acyl, alkyl, aryl, urea, phthalimide (with R1 = ö), biotin, or the group A can form with the nitrogen atom with which it is contiguous an NH2+ entity,

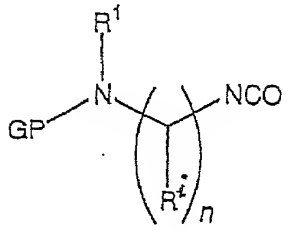
- Zk, Z'k, Fk and F'k represent independently of each other a hydrogen atom, a protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a halogen, a (C1-C20) alkyl group, substituted or not, or an aryl group.

Amend claim 12 as follows:

--12. (amended) Compounds according to claim 9, having the formula (Ibis) in which 1<n<4, and is particularly from p-nitrophenol, N-hydroxysuccinimide, pentafluorophenol, hydroxy-1,2,3-benzotriazole or imidazole, GP is an oxycarbonyl group or acyl group.

Amend claim 16 as follows:

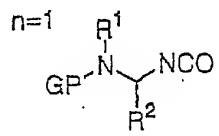
--16. (amended) Compounds according to claim 15, having the formula (II):

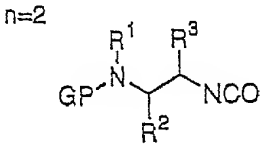


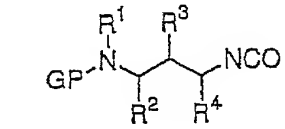
(II)

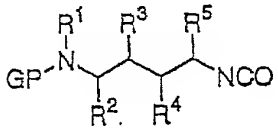
Amend claim 18 as follows:

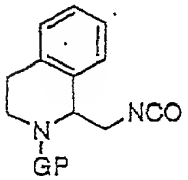
--18. (amended) Compounds according to claim 16, having the formula (II) in which 1 < n < 4, GP is an oxycarbonyl group or acyl group, and particularly the following compounds, in particular those for which GP - Boc and Fmoc:

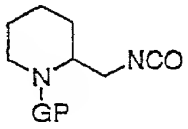


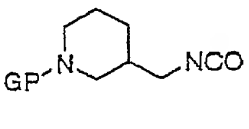


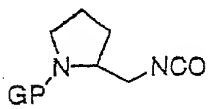


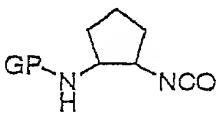


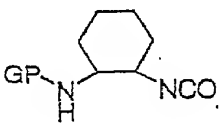


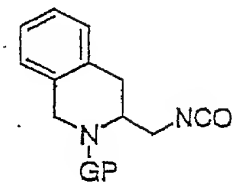


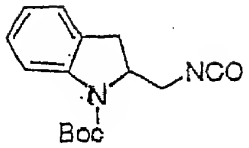






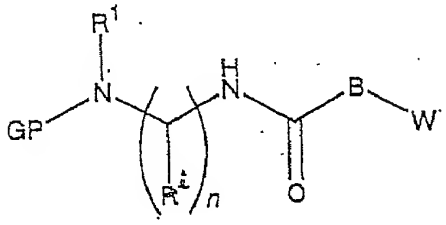






Amend claim 20 as follows:

--20. (amended) Compounds according to claim 19, having the formula (VI):



(VI)

Amend claim 27 as follows:

--27. (amended) Compounds according to claim 7, in which the aryl group can be substituted with 1 to 6 substituents selected from: alkyl, alkoxy, amine, ester, urea, amide, carboxylic acid, 1 to 10 carbon atoms, hydroxyl, nitrile, nitro, guanidine, aryl whose cyclic structure contains 5 to 20 carbon atoms, and a halogen atom.

Amend claim 28 as follows:

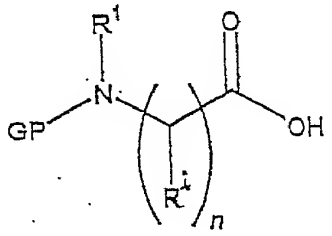
--28. (amended) Compounds according to claim 7, in which the alkyl group is substituted with one or several substituents selected from the groups: -COORh, -CONHRh, -COOH, -OH, -ORh, -NHRh, -NH2, -NH(CO)Rh, aryl whose cyclic structure contains 5 to 20 carbon atoms, halogen, carbonyl of 1 to 10 carbon atoms, nitrile, guanidine,

Rh representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

Amend claim 29 as follows:

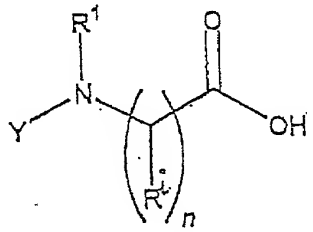
--29. (amended) Process for preparation of derivatives corresponding to the formulas (I bis), (II), (III bis) or (IV) according to claim 7, from respectively:

- compounds of formula (IX) (for compounds of formula (I bis) and (II))



(IX)

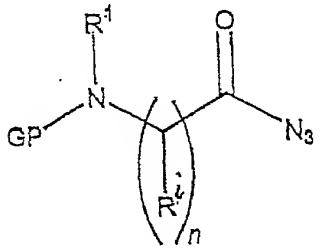
- compounds of formula (X) (for compounds of formula (III bis) and (IV))



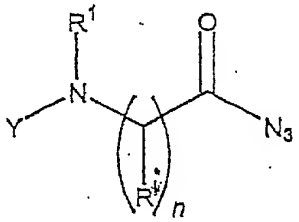
(X)

comprising

(a) a step of transformation of acid (IX) or (X) into the corresponding acyl azide (XII) or (XIII) respectively



(XII)



(XIII)

by a suitable treatment,

(b) a step of transformation of acyl azide (XII) or (XIII) by Curtius rearrangement into the corresponding isocyanate (II) or (IV) respectively,

(c) a step of treatment of isocyanate (II) or (IV), preferably not isolated, under conditions permitting obtaining a carbamic acid derivative of formula (I bis) or (III bis).

Amend claim 31 as follows:

--31. (amended) Process for preparation of compounds according to claim 19, comprising the reaction of compounds containing primary or secondary amines or alcohols with one of the products of formula (I bis), (II), (III bis) or (IV) in a solvent, with or without the addition of an organic or mineral base.

R E M A R K S

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,
YOUNG & THOMPSON

By _____
Andrew J. Patch
Attorney for Applicant
Registration No. 32,925
Customer No. 00466
745 South 23rd Street
Arlington, VA 22202
Telephone: 703/521-2297

July 16, 2001

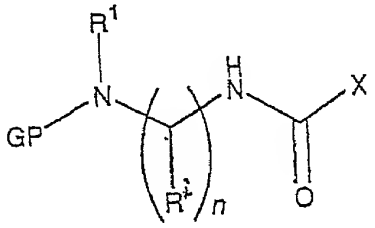
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amend claim 3 as follows:

--3. (amended) Process according to claim 1~~ or 2~~, in which the structure of the activated derivative of carbamic acid is conferred by the N-hydroxysuccinimide group.

Amend claim 9 as follows:

--9. (amended) Compounds according to claim 7~~ or 8~~, having the formula (I bis)

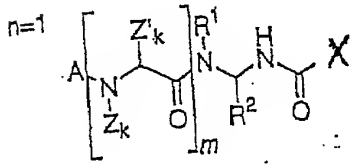


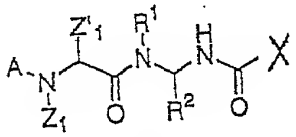
(I bis)

~~in which n, i, GP, X, R1 and Ri have the meanings given in claims 7 or 8.~~

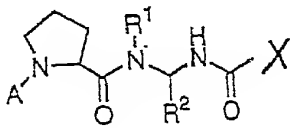
Amend claim 10 as follows:

--10. (amended) Compounds according to claim 7~~ or 8~~, having the following formulas:

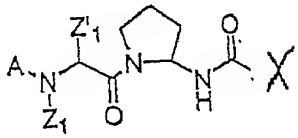




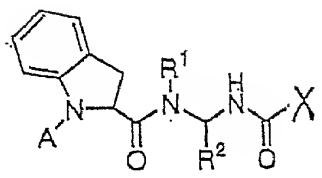
m =1



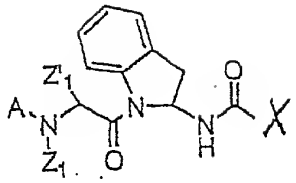
m =1



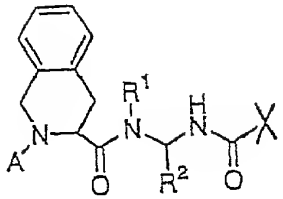
m =1



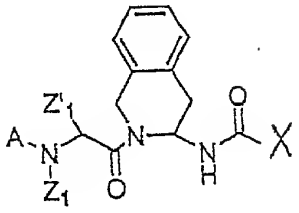
m =1



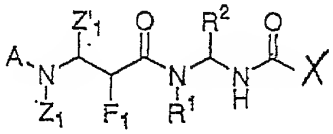
m =1



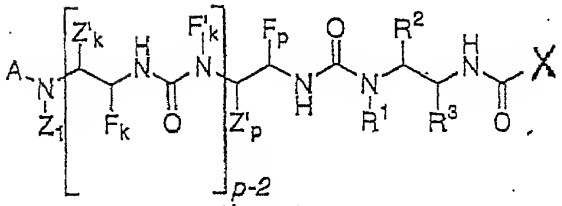
m =1



m =1

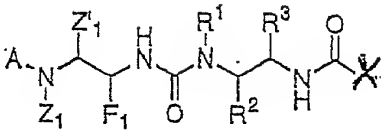


n=2

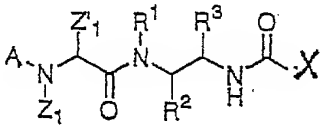


p-2

k varying from 2 to p-1



p=1



in which

- m and p are comprised from 1 to 10,

- A represents either a protective group selected from the following groups: a hydrogen atom, an oxycarbonyl (ROCO) group, acyl, alkyl, aryl, urea, phthalimide (with R1 = ö), biotin, or the group A can form with the nitrogen atom with which it is contiguous an NH2+ entity,

- Zk, Z'k, Fk and F'k represent independently of each other a hydrogen atom, a protected or unprotected side

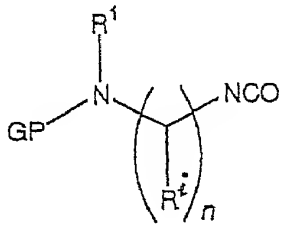
chain of an amino acid selected from natural and synthetic amino acids, a halogen, a (C1-C20) alkyl group, substituted or not, or an aryl group.

Amend claim 12 as follows:

--12. (amended) Compounds according to claim 9, having the formula (Ibis) in which 1<n<4, ~~X is as defined in claim 7~~ and is particularly from p-nitrophenol, N-hydroxysuccinimide, pentafluorophenol, hydroxy-1,2,3-benzotriazole or imidazole, GP is an oxycarbonyl group or acyl group ~~as defined in claim 7~~.

Amend claim 16 as follows:

--16. (amended) Compounds according to claim 15, having the formula (II):

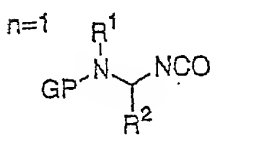


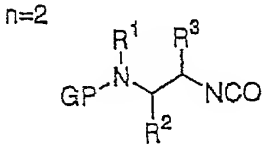
(II)

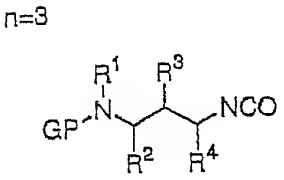
~~in which n, i, GP, R1 and Ri have meanings mentioned in claim 15~~.

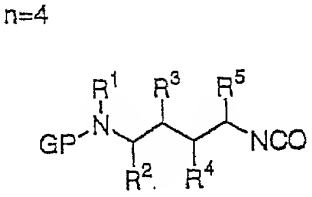
--18. (amended) Compounds according to claim 16, having the formula (II) in which 1 < n < 4, GP is an oxycar-

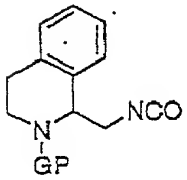
bonyl group or acyl group ~~such as defined in claim 15~~, and particularly the following compounds, in particular those for which GP - Boc and Fmoc:

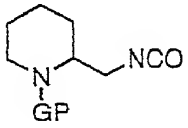


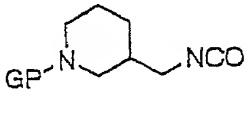


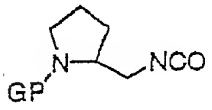


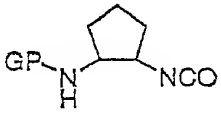


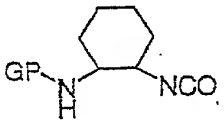


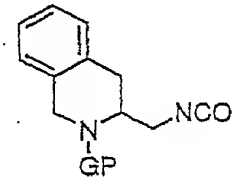


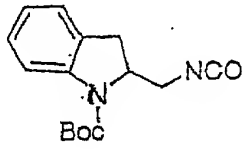






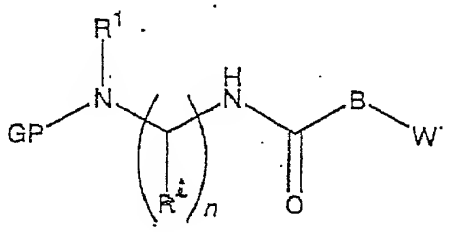






Amend claim 20 as follows:

--20. (amended) Compounds according to claim 19, having the formula (VI):



(VI)

~~in which n, i, GP, R1, Ri, B and W have the meanings mentioned in claim 19.~~

Amend claim 27 as follows:

--27. (amended) Compounds ~~having one of the formulas (I bis), (II), (III bis), (IV), (VI), (VII)~~ according to ~~one of claims~~ claim 7 ~~to 22~~, in which the aryl group can be substituted with 1 to 6 substituents selected from: alkyl, alkoxy, amine, ester, urea, amide, carboxylic acid, 1 to 10 carbon atoms, hydroxyl, nitrile, nitro, guanidine, aryl whose cyclic structure contains 5 to 20 carbon atoms, and a halogen atom.

Amend claim 28 as follows:

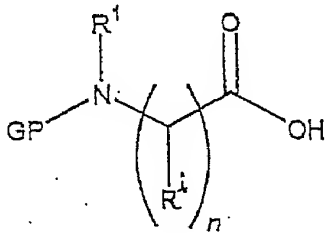
--28. (amended) Compounds according to ~~one of claims~~ claim 7~~, 15, 19 or 25~~, in which the alkyl group is substituted with one or several substituents selected from the groups: -COORh,
-CONHRh, -COOH, -OH, -ORh, -NHRh, -NH2, -NH(CO)Rh, aryl whose cyclic structure contains 5 to 20 carbon atoms, halogen, carbonyl of 1 to 10 carbon atoms, nitrile, guanidine,

Rh representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

Amend claim 29 as follows:

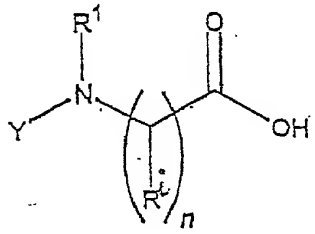
--29. (amended) Process for preparation ~~according to one of claims 1 to 3,~~ of derivatives ~~corresponding to the formulas (I bis), (II), (III bis) or (IV)~~ according to ~~one of claims~~ claim 7 ~~to 18~~, from respectively:

- compounds of formula (IX) (for compounds of formula (I bis) and (II))



(IX)

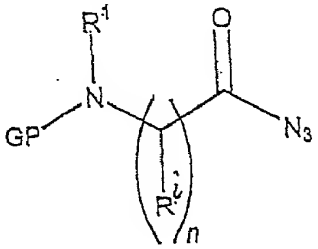
- compounds of formula (X) (for compounds of formula (III bis) and (IV))



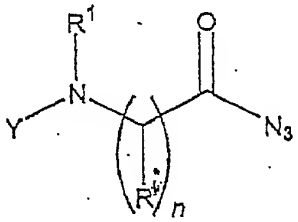
(X)

comprising

(a) a step of transformation of acid (IX) or (X) into the corresponding acyl azide (XII) or (XIII) respectively



(XII)



(XIII)

by a suitable treatment,

(b) a step of transformation of acyl azide (XII) or (XIII) by Curtius rearrangement into the corresponding isocyanate (II) or (IV) respectively,

(c) a step of treatment of isocyanate (II) or (IV), preferably not isolated, under conditions permitting obtaining a carbamic acid derivative of formula (I bis) or (III bis).

Amend claim 31 as follows:

--31. (amended) Process for preparation ~~according to claim 1,~~ of compounds ~~of formula (VI) or (VII)~~ according ~~to one of claims~~ claim 19 ~~to 22~~, comprising the reaction of compounds containing primary or secondary amines or alcohols with one of the products of formula (I bis), (II), (III bis)

or (IV) ~~according to one of claims 7 to 18,~~ in a solvent, with or without the addition of an organic or mineral base.